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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/071,032	02/08/2002	Richard Dennis Dyer	A0000425-01-CFP	3659

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EXAMINER	
TRUONG, TAMTHOM NGO	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 05/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/071,032	DYER ET AL.	
	Examiner	Art Unit	
	Tamthom N. Truong	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 (in part), 7-32 (in part), and 34-44 (in part)* is/are pending in the application.

4a) Of the above claim(s) *5, 6, and 33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,7-9,11-14,21-32,34 and 36-44* is/are rejected.

7)☒ Claim(s) *4,10,15-20 and 35* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5,9,13*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election of Group I (claims 1-4 (in part), 7-32 (in part), and 34-44 (in part) in the response of 2-18-04 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 5, 6, and 33 are withdrawn from consideration as being drawn to non-elected subject matter.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-3, 7-9, 11-14, 21-32, 34, and 36-44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1-3, 11-14, 30-32, 34 recite the word "*substituted*" in front of the moiety (e.g., "substituted C_1-C_6alkyl", "substituted C_2-C_6 alkenyl", etc.) which renders indefinite metes and bounds for those claims because there is no substituents listed for those "*substituted*" moieties. In the absence of the specific moieties intended to effectuate modification by "substitution" or attachment to the chemical core claimed, the term "substituted" renders the claims in which it appears indefinite in all occurrences wherein

applicant fails to articulate by chemical name, structural formula or sufficiently distinct functional language, the particular moieties applicant regards as those which will facilitate substitution, requisite to identifying the composition of matter claimed.

b. Claims 21-29, and 36-44 are rejected as being dependent on claims 1, or 30-34, and are carrying over limitations that are (generally) "*substituted*".

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. **Scope of Enablement:** Claims 22-25, 28, 41, and 42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the method of treating inflammation, rheumatoid arthritis, and osteoarthritis, does not reasonably provide enablement for other diseases that are allegedly related to MMP-13 (e.g., cancer, heart failure, etc.). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The following factors have been considered in the determination of an enabling disclosure:

(1) The breadth of the claims;

(2) The amount of direction or guidance presented;

(3) The state of the prior art;

(4) The relative skill of those in the art;

(5) The predictability or unpredictability of the art;

(6) The quantity of experimentation necessary;

[See ***Ex parte Forman***, 230 USPQ 546 (Bd. Pat. App. & Int., 1986); also ***In re Wands***, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)].

a. The breadth of the claims: Claims 22, 23, and 41 recite a method for inhibiting MMP-13, or treating a disease mediated by MMP-13. Such a method covers the treatment of an array of diseases-- both known and unknown presently. Claims 24, 25, and 42 recite a method for treating a cancer, or breast carcinoma, which is supposedly associated with MMP-13. Claim 28 recites a method for treating heart failure, which also appears to be related to MMP-13. However, MMP-13 is one of collagenase enzymes that is known to treat inflammation at the most. Thus, the scope of claims 22-28, 28, 41, and 42 include methods for treating diseases that might not have MMP-13 as the underlined causative factor.

b. The amount of direction or guidance presented: The specification does not provide data or evidence that relates MMP-13 to the treatment of cancer, breast carcinoma, heart failure, or any other diseases. For a compound to inhibit MMP-13 *in-vitro* does not mean it can treat any disease that is suspected to be related to MMP-13.

c. The state of the prior art: As indicated the article of **Greenwald**, the problem in developing an effective MMP inhibitor lies in the poor *in vivo* efficacy as well as a poor safety profile. Consider the following excerpt:

> *The problem is that the chemistry appears to have outstripped the biology. In vitro, there are many inhibitors with nanomolar or picomolar efficacy, but in vivo efficacy in animal models does not always follow. {Abstract}*

Thus, it is clear that *in-vitro* data alone does not allow a skilled clinician to apply the claimed compound in the treatment of cancer, heart failure, or any disease that is suspected to be related to MMP-13.

d. The predictability or unpredictability of the art: The pharmaceutical art has always been an unpredictable art. Consider the following statement from the article of Greenwald:

> *Discovering an active compound is relatively easy, but discovering an important new drug remains unbelievably difficult.*

Thus, with the limited guidance provided, and the unpredictable nature of the art, it would require undue experimentation for the skilled clinician to treat MMP mediated diseases other than inflammation, rheumatoid arthritis, and osteoarthritis.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1-3, 8, 9, 21, 30 and 36 are rejected under 35 U.S.C. 102(b) as being anticipated by **Furrer et. al.** (DE 41 37 437—cited on IDS). In Table 1, Furrer et. al. disclose several compounds (e.g. compounds # 3, 5, 7, 16, 17, and 24) that read on the following claims:

a. Claims 1 and 30: the compound of formula I with the following substituents:

i. X is S, or SO; Y is O;

ii. R^1 (corresponds to R^2 of the reference) represents either hydrogen or an alkyl group;

iii. R^2 and R^3, each is hydrogen;

iv. R^4 represents a substituted alkyl group, or $(CH_2)_mOR^5$, wherein m = 1, and R^5 is an alkyl group;

b. Claim 2: the compound of formula II with the following substituents:

i. X is S, or SO;

ii. R^1 (corresponds to R^2 of the reference) represents either hydrogen or an alkyl group;

iii. R^2 and R^3, each is hydrogen;

iv. R^4 represents a substituted alkyl group, or $(CH_2)_mOR^5$, wherein m = 1, and R^5 is an alkyl group;

c. Claim 3: the compound of formula III with the following substituents:

i. R^1 (corresponds to R^2 of the reference) represents either hydrogen or an alkyl group;

ii. R^2 and R^3, each is hydrogen;

iii. R^4 represents a substituted alkyl group, or $(CH_2)_mOR^5$, wherein m = 1, and R^5 is an alkyl group;

d. Claim 8: the compound of formula VI with the following substituents:

i. X is S, or SO; Y is O;

ii. R^1 (corresponds to R^2 of the reference) represents either hydrogen or an alkyl group;

iii. R^2 and R^3, each is hydrogen;

iv. R^4 represents a substituted alkyl group, or $(CH_2)_mOR^5$, wherein m = 1, and R^5 is an alkyl group;

e. Claim 9: the compound of formula VII with the following substituents:

i. X is SO;

ii. R^1 (corresponds to R^2 of the reference) represents either hydrogen or an alkyl group;

iii. R^2 and R^3, each is hydrogen;

iv. R^4 represents a substituted alkyl group, or $(CH_2)_mOR^5$, wherein m = 1, and R^5 is an alkyl group;

f. Claims 21 and 39: the pharmaceutical composition comprising a compound of formula I in claims 1 and 30 (see supra).

5. Claims 1-3, 8, 9, 21, 26, 27, 29, 30, and 36 are rejected under 35 U.S.C. 102(b) as being anticipated by **Naka et. al.** (US 5,082,838—cited on IDS). Naka et. al. disclose several compounds (e.g. columns 23-24, compounds # 2, 4, 5, etc., columns 29-30, compound # 47, columns 41-42, compounds #95-97) that read on the following claims:

a. Claims 1 and 30: the compound of formula I with the following substituents:

i. X is S, or SO; Y is O;

ii. R^1 (corresponds to R^2 of the reference) represents either hydrogen or – NR^5R^6 (wherein R^5 and R^6, each represents hydrogen or an alkyl group);

iii. R^2 and R^3, each is hydrogen;

iv. R^4 (corresponds to R^1 of the reference) represents an alkyl group,

b. Claim 2: the compound of formula II with the following substituents:

i. X is S, or SO;

ii. R^1 (corresponds to R^2 of the reference) represents either hydrogen or – NR^5R^6 (wherein R^5 and R^6, each represents hydrogen or an alkyl group) ;

iii. R^2 and R^3, each is hydrogen;

iv. R^4 represents an alkyl group,

c. Claim 3: the compound of formula III with the following substituents:

i. R^1 (corresponds to R^2 of the reference) represents either hydrogen or – NR^5R^6 (wherein R^5 and R^6, each represents hydrogen or an alkyl group);

ii. R^2 and R^3, each is hydrogen;

iii. R^4 represents an alkyl group,

d. Claim 8: the compound of formula VI with the following substituents:

i. X is S, or SO; Y is O;

ii. R^1 (corresponds to R^2 of the reference) represents either hydrogen or – NR^5R^6 (wherein R^5 and R^6, each represents hydrogen or an alkyl group);

iii. R^2 and R^3, each is hydrogen;

iv. R^4 represents an alkyl group,

e. Claim 9: the compound of formula VII with the following substituents:

i. X is SO;

ii. R^1 (corresponds to R^2 of the reference) represents either hydrogen or – NR^5R^6 (wherein R^5 and R^6, each represents hydrogen or an alkyl group);

iii. R^2 and R^3, each is hydrogen;

iv. R^4 represents an alkyl group,

f. Claims 21 and 36: the pharmaceutical composition comprising a compound of formula I in claims 1 and 30 (see supra).

b. Claims 26, 27, and 29: the method of treating a rheumatoid arthritis, osteoarthritis, and an inflammation by administering a compound of claim 1. Since the disclosed compound can treat inflammatory diseases such as rheumatism.

6. Claims 1-3, 8, 21, 30, and 36 are rejected under 35 U.S.C. 102(b) as being anticipated by **Kaul et. al.** (J. Pharm. Sci.—cited on IDS). Metabolite #4 on page 900 reads on the following claims:

a. Claims 1 and 30: the compound of formula I with the following substituents:

i. X is S, and Y is O;

ii. R^1 and R^4, each represents an alkyl group;

iii. R^2 is $(CH_2)_mOH$;

iv. R^3 is hydrogen;

b. Claim 2: the compound of formula II with the following substituents:

i. X is S

ii. R^1 and R^4, each represents an alkyl group;

iii. R^2 is $(CH_2)_mOH$;

iv. R^3 is hydrogen;

c. Claim 3: the compound of formula III with the following substituents:

i. R^1 and R^4, each represents an alkyl group;

ii. R^2 is $(CH_2)_mOH$;

iii. R^3 is hydrogen;

d. Claim 8: the compound of formula VI with the following substituents:

i. X is S, and Y is O;

ii. R^1 and R^4, each represents an alkyl group;

iii. R^2 is $(CH_2)_mOH$;

iv. R^3 is hydrogen;

e. Claim 21: the pharmaceutical composition comprising a compound of claim 1 is inherently taught because the disclosed compound is a metabolite.

f. Claim 36: the pharmaceutical composition comprising a compound of claim 1 is inherently taught because the disclosed compound is a metabolite.

7. Claims 1-3, 8, 21, 30, and 36 are rejected under 35 U.S.C. 102(b) as being anticipated by **Kaul et. al.** (Xenobiotica—cited on IDS). Compound VI on page 496 reads on the following claims:

a. Claims 1 and 30: the compound of formula I with the following substituents:

i. X is S, and Y is O;

ii. R^1 and R^4, each represents an alkyl group;

iii. R^2 is $(CH_2)_mOH$;

iv. R^3 is hydrogen;

b. Claim 2: the compound of formula II with the following substituents:

i. X is S

ii. R^1 and R^4, each represents an alkyl group;

iii. R^2 is $(CH_2)_mOH$;

iv. R^3 is hydrogen;

c. Claim 3: the compound of formula III with the following substituents:

i. R^1 and R^4, each represents an alkyl group;

ii. R^2 is $(CH_2)_mOH$;

iii. R^3 is hydrogen;

d. Claim 8: the compound of formula VI with the following substituents:

i. X is S, and Y is O;

ii. R^1 and R^4, each represents an alkyl group;

iii. R^2 is $(CH_2)_mOH$;

iv. R^3 is hydrogen;

e. Claim 21: the pharmaceutical composition comprising a compound of claim 1 is inherently taught because the disclosed compound is a metabolite.

f. Claim 36: the pharmaceutical composition comprising a compound of claim 1 is inherently taught because the disclosed compound is a metabolite.

8. Claims 1-3, 8, 21, 30, and 36 are rejected under 35 U.S.C. 102(b) as being anticipated by **Kaul et. al.** (Arzneim.-Forsch—cited on IDS). Compound VI on the right column of page 611, reads on the following claims:

a. Claims 1 and 30: the compound of formula I with the following substituents:

i. X is S, and Y is O;

ii. R^1 and R^4, each represents an alkyl group;

iii. R^2 is $(CH_2)_mOH$;

iv. R^3 is hydrogen;

b. Claim 2: the compound of formula II with the following substituents:

i. X is S

ii. R^1 and R^4, each represents an alkyl group;

iii. R^2 is $(CH_2)_mOH$;

iv. R^3 is hydrogen;

c. Claim 3: the compound of formula III with the following substituents:

i. R^1 and R^4, each represents an alkyl group;

ii. R^2 is $(CH_2)_mOH$;

iii. R^3 is hydrogen;

d. Claim 8: the compound of formula VI with the following substituents:

i. X is S, and Y is O;

ii. R^1 and R^4, each represents an alkyl group;

iii. R^2 is $(CH_2)_mOH$;

iv. R^3 is hydrogen;

e. Claim 21: the pharmaceutical composition comprising a compound of claim 1 is inherently taught because the disclosed compound is a metabolite.

f. Claim 36: the pharmaceutical composition comprising a compound of claim 1 is inherently taught because the disclosed compound is a metabolite.

9. Claim 30 is rejected under 35 U.S.C. 102(b) as being anticipated by **Tsuge et. al.** (Tetrahedron, 1972, Vol. 28, pp. 4737-46). On page 4742, Tsuge et. al. disclose compound #27 which reads on the compound of formula I in claim 30 with the following substituents:

v. R^2, R^3, and R^4 – each represents hydrogen;

vi. R^1 is an alkyl group.

Note, claim 30 does not have the proviso in claim 1, and therefore, does not exclude compound #27 of Tsuge et. al.

Claim Objections

10. Claims 4, 10, 15-20, and 35 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Said claims recite species with substituents that are not taught in the prior arts of record.

Information Disclosure Statement

The IDS of 06-17-02 has been considered for all references, except two Derwent abstracts, which are not provided.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tamthom N. Truong whose telephone number is 571-272-0676. The examiner can normally be reached on M-F (~10 am ~ 6:30 pm).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mukund Shah can be reached at 571-272-0674. If you are unable to reach Dr. Shah within a 24 hour period, please contact James O. Wilson, Acting SPE of 1624, at 571-272-0661.

The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

RICHARD L. RAYMOND
PRIMARY EXAMINER
ART UNIT 1624

T. Truong
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May 13, 2004